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BULLETIN OF
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ON HERBICIDAL ACTIONS

I. OPATOWSKI AND ALICE M. CHRISTIANSEN
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A theoretical interpretation of the herbicidal action of the 2,4-Dichlorophenoxyacetic acid is suggested.

It was the idea of P. Jordan (1941) to interpret certain biological effects as due to a random event consisting of a penetration of a molecule of an external agent into a vital center of the organism (v. Schelling, 1942). It is the purpose of the present note to point out that the experimental results of J. van Overbeek, L. E. Gregory and I. Vélez (1946) on the herbicidal action of water solution of 2,4-Dichlorophenoxyacetic acid are in agreement with these concepts, if such action is attributed to a single molecule or to a single aggregate of molecules of the acid reaching a particular center of the plant. No direct experimental evidence of such mechanism can be obtained, at least with the presently known techniques. Some indication of its possibility may be seen in the known general fact of translocation of the chlorophenoxy compounds within the plants (Zimmerman and Hitchcock, 1942). Other indications are found in the specific experiment of J. van Overbeek, L. E. Gregory, and I. Vélez (1946) consisting of painting a leaf of shoots of commelina with a solution of 2,4-D, which produced the death of a stem region 10 cm below the treated leaf and did not affect the stem above the leaf. According to these authors, 2,4-D does not burn the foliage but acts internally on a well-defined region of the plant.

The following theory is suggested for an interpretation of the quantitative results of J. van Overbeek and his co-workers: Let a homogeneous aggregate of plants be sprayed with a solution of concentration C, the concentration being measured in volume. C is the total volume of the molecules of the acid per 1 cm^3 of the solution. Let S be the total volume of the above mentioned sensitive vital centers of the plant and R the volume of a region in the plant containing those centers and such that the solution does not penetrate in the plant beyond that region. The region R may be the whole volume of the plant. Let V be the volume of the solution in R. If M cm^3 is the volume of one molecule of the acid, there are C/M molecules of the acid per 1 cm^3 of the solution, i.e., the average volume of the solution containing 1 molecule of the acid is M/C cm^3. If $V = R$, i.e., if the solution penetrates the whole region R and consequently the whole volume S, then SC/M is the average number of molecules of the acid in S cm^3. If the volume V of the solution in R is smaller than R, then in S cm^3 of R there is an average of $(V/R)S$ cm^3 of solution and the average number of molecules of the acid in S cm^3 is $VSC/(MR)$. The maximum possible number of molecules of the acid in S cm^3 is S/M. Consequently, if we divide the volume S into S/M parts of M cm^3 each, the probability that a molecule of the acid reach one such particular part is represented by

$$VSCM^{-1}R^{-1}/SM^{-1} = VC/R\,. \tag{1}$$

The probability that no molecule of the acid reach that particular part of S is $1-VCR^{-1}$, and the probability that no acid molecule reach any of the above parts of S is

$$(1 - VCR^{-1})^{S/M}\,. \tag{2}$$

The probability P that at least one molecule of the acid reach S is:

$$P = 1 - (1 - VCR^{-1})^{S/M}\,. \tag{3}$$

Since $(1+y)^z \approx \exp(yz)$, for small y and large z, we obtain under the assumptions of small concentration C and a large sensitive volume with respect to the volume of one acid molecule:

$$P \approx 1 - \exp(-VCSR^{-1}M^{-1})\,. \tag{4}$$

The above reasoning follows to some extent the pattern used by M. A. Lauffer and W. C. Price (1945) in the study of infection by viruses. The theory presented here disregards the possibility that the solution may be eliminated from the plant through natural processes and that new solution may take its place. The possibility of recovery of the sensitive volume to its original condition is also not taken into account. The probability P represents what J. van Overbeek and I. Vélez (1946a) call the "mortality" of the plant, if the time between the occurrence of the critical event (e.g., combination of a molecule of the acid with a particular organic molecule of a plant cell) and the appearance of the external effect (e.g., destruction of a growing region of the plant) is smaller than the interval of time between the spraying of the plants and the counting of the dead ones, and if the latter interval of time is sufficiently long so that no further translocation of the solution within the plant occurs.

A comparison of the values of P calculated from the above formula with the experimental results of J. van Overbeek and I. Vélez (1946a) is given in the table below. Those authors published their results in form of smooth thick curves which give for each value of concentration a range of values of mortality. The curves are clearly of an exponential type, as it is required by the probabilistic theory based on a "single effective event" type of process. It is seen from the table that the fit is good, although working directly on experimental figures rather than on the smoothed curves could lead to more definite conclusions.

In the following table C denotes the concentration of the acid and $k = VR^{-1}\,SM^{-1}$.

	COMMELINA		AMARANTHUS		CYPERUS	
1000 C	Experimental Range of P	P Calculated with $k = 6360$	Experimental Range of P	P Calculated with $k = 2620$	Experimental Range of P	P Calculated with $k = 1040$
0.25	0.80 – 0.87	0.80	0.47 – 0.50	0.48	0.18 – 0.27	0.23
0.375	0.90 – 0.92	0.91	0.60 – 0.63	0.63	0.29 – 0.32	0.32
0.50	0.94 – 0.96	0.96	0.68 – 0.73	0.73	0.39 – 0.41	0.40
0.75	0.98 – 0.99	0.99	0.84 – 0.87	0.86	0.53 – 0.56	0.54
1.00			0.91 – 0.93	0.93	0.64 – 0.67	0.65
1.25			0.94 – 0.97	0.96	0.72 – 0.74	0.73
1.50			0.98 – 0.99	0.98	0.79 – 0.81	0.79
2.00					0.88 – 0.90	0.88
2.50					0.93 – 0.96	0.93
3.00					0.96 – 0.98	0.96

The knowledge of k makes it possible to estimate the total sensitive volume S in a plant:

$$S = (R/V)Mk \quad \text{or} \quad S \geqq Mk\,. \tag{5}$$

If the experiments are carried out *in condition of saturation,* that is, with such an amount of solution that any further increase of this amount does not modify the mortality, then $V = R$ and $S = Mk$. *The sensitive volume is then simply* k *times the volume of one molecule of the acid.* If this condition was fulfilled in the experiments in question, then the sensitive volume in each plant was from about 1000 to about 6000 times the size of a single molecule of the 2,4-Dichlorophenoxyacetic acid. However, an estimate of the volume of a molecule is a difficult problem. Moreover, a definition of that volume independently of the nature of the sensitive center does not seem possible, because both the volume of the molecule of the acid and that of a molecule of the sensitive substance, as they are used in the present theory, are regions of space bound to those molecules and characterized by the fact that a mutual contact of these two regions leads to the event observed, for instance, through a single chemical reaction or through a chain of such reactions. Such definition may be still incomplete, because it does not take into account the fact that the occurrence of a certain chemical reaction may depend not only on an overall distance, but also on a particular reciprocal orientation of the two molecules.

In any way, routine computations of the molecular volume (cf. Glasstone, 1940) give a figure of about 300 Å^3 per molecule of the 2,4-Dichlorophenoxyacetic acid. Very rough estimates based on interatomic distances (cf. Stuart, 1934) give a round figure of 50 Å^3. If 300 Å^3 is taken for M, the total sensitive volume existing in each plant is $S \geqq 300k$ Å^3, which is about 3×10^{-19} cm^3 to 2×10^{-18} cm^3, depending on the species of the plant. This is an extremely small amount if compared, for instance, with the 10^{-6} gr. of auxin existing in yeast per each gram of dry weight (Kögl and Haagen Smit, 1931; Kögl, 1933).

Dr. H. D. Landahl has kindly pointed out to the writers that the above theory does not take into account the existence of a threshold concentration of 2,4-D. Such concentration has been actually given by P. W. Zimmerman (1943). In this connection it should be kept in mind that the threshold concentrations are extremely low. Those given by P. W. Zimmerman are some six thousand times smaller than the maximum concentration used by the same author in the same set of experiments. Experimentation with such low concentrations is very inaccurate unless a very large sample is used.

The authors are indebted to Professor H. D. Landahl of the University of Chicago for his enlightening criticism, to Professor F. G. Gustafson of the Department of Botany of the University of Michigan for suggesting invaluable references and to Professor K. Fajans for his kindness in discussing some general questions of chemistry connected with the present subject.

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ON MATRICES OF NEURAL NETS

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The structure of a complete or incomplete neural net is represented here by several matrices. The activity equation of the net follows in a general form. A chain or cycle is defined as a neural structure whose connection matrix is unitary. We can compute the number of simple chains by a recurrent formula.

In a paper by H. D. Landahl and Richard Runge (1946), the activity of a neural net is represented in terms of a matrix vector equation in which the matrix represents the structure of the net. Here we represent the structure of a net by several matrices which have their own peculiar significances.

We shall make the following physical assumptions for our neuron-nets:

1) The *activity* of the neuron is of the *all-or-none* character.

2). A neuron can be excited into *all-activity* either by the actions of other neurons connected to it or by an external stimulus. An afferent neuron is one stimulated by an appropriate external stimulus. An internal neuron is stimulated only by other neurons. An internal neuron fires if and only if a sufficient number of end bulbs terminating on it fire within the *period of latent addition.* The minimum number of terminal bulbs which must fire within the period of latent addition in order to make the neuron fire is called the threshold of the neuron. The threshold is considered as a constant independent of the previous activity of the neuron. The all-activity of a neuron is always of the same *intensity* through every branch of its axone.

3) The all-activity of a neuron lasts throughout its *time of action.*

4) The *synaptic* delay is the same for all neurons in a neuron-net and is the only significant delay in the nervous system when it is compared with the period of latent addition, the time of action and the *conduction time.* For convenience, the interval of synaptic delay will be considered as a unit time.

5) No neuron acts upon itself.

6) In the configuration of our network we think of the *resultant effect* of all excitatory and inhibitory synapses from neuron N_i directly to neuron N_j as a *single action* through a *single fiber*, $||i\ j||$. The action is positive, negative or zero according to whether it is purely excitatory, purely inhibitory or has no effect at all. Any action from the same source to the same object directly, i.e., no neurons lying in between, is also considered as through a single fiber.

General Activity Equation. By a *complete net* we mean that no other neurons or other fibers outside of this net are associated with it; otherwise, it is incomplete. Let N be a net of n ordered neurons $(N_1, N_2, \cdots, N_n)$, complete or incomplete. Let

$s_i(t)$ = the intensity of external stimulus acting upon N_i at the time t,

n_{ij} = the non-negative intensity of stimulus through $||i\ j||$,

$$d_{ij} = \begin{cases} +1 \\ -1 \quad \text{when} \quad ||i\ j|| \\ 0 \end{cases} \begin{cases} > 0, \\ < 0, \\ = 0, \end{cases}$$

$t_{ij} = d_{ij}\, n_{ij}$,

h_i = threshold of N_i,

According to our assumption, $d_{ii} = n_{ii} = t_{ii} = 0$ for $i = 1, 2, \cdots, n$. We define

$a(t) = (a_1(t), a_2(t), \cdots, a_n(t))$

= the *activity vector* of N, as defined by Landahl and Runge,

$E = (n_{ij})$ = the *intensity matrix* of N,

$D = (d_{ij})$ = the *connection matrix* of N,

$T = (t_{ij})$ = the *structural matrix* of N,

$$H = \begin{vmatrix} 1/h_1 & 0 & \ldots & 0 \\ 0 & 1/h_2 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots \\ 0 & \ldots & \ldots & 1/h_n \end{vmatrix}$$ = *the diagonal inverse threshold-matrix of* N.

The scalar quantity

$$v_i(t) = \frac{1}{h_i}\left(s_i(t) + \sum_{j=1}^{j=n} a_j(t-1)\, n_{ji}\, d_{ji}\right)$$

measures the *excitation state* of N_i at time t. The vector

$$v(t) = (v_1(t), \cdots, v_n(t)) = (a(t-1)\ T + s(t))H$$

measures the *excitation pattern* of N, where $s(t) = (s_1(t), \cdots, s_n(t))$. A quantity q can sometimes be *normalized* in the following way:

$$[q] = \begin{cases} q & \text{when} \quad q \geqq 1\,, \\ 0 & \text{when} \quad q < 1\,. \end{cases}$$

A matrix is said to be normalized and denoted by the similar notation if we normalize all its elements.

We have thus the activity equation of N,

$$a(t) = [v(t)] = [(a(t-1)T + s(t))H]\,. \tag{1}$$

Chains and Cycles. A complex C_m of m neurons and m associated fibers in a net constitutes a *simple (structural) chain of order m* if each neuron receives fibers from only one neuron and sends fibers to only one neuron. A simple chain is called a *cycle* if it cannot be reduced to two or more simple chains.

A mathematical representation of simple chains and cycles can be obtained from the following theorems:

THEOREM 1. *The necessary and sufficient condition for a complex* $\mathrm{C_m}$ *in a net to be a simple chain is that the connection matrix* D *of* $\mathrm{C_m}$ *is unitary, i.e.,* $\mathrm{DD^* = D^*D = e}$, *where* $\mathrm{D^*}$ *is the transpose of* D *and* e *is the unit matrix of order* m. (See Pontrjagin 1939, p. 108.)

In fact, C_m is a simple chain if and only if there is one and only one element different from zero, viz., +1 or —1, in each row and in each column of its connection matrix D. Therefore, if and only if

$$\sum_{i=1}^{m} d_{ij}\, d_{ik} = \delta_{jk} \qquad (\delta_{ii} = 1, \qquad \delta_{ij} = 0 \text{ for } i \neq j)\,.$$

THEOREM 2. *A simple chain of order* m *can be decomposed into a finite system of disconnected cycles of which the sum of orders is equal to* m *if and only if its connection matrix is reducible. Every cycle of order* r *is represented by an irreducible unitary connection matrix of order* r.

By rearranging the order of neurons in a simple chain of order m, we can always have the connection matrix in the new form

$$t^{-1} D\, t = \begin{pmatrix} a & 0 \\ 0 & b \end{pmatrix},$$

where t is non-singular. The submatrices a and b are also unitary and represent two disconnected simple chains. The sum of the orders of a and b is m. If a or b is still reducible, it in turn may be further decomposed. In this way we get finally a finite system of irreducible submatrices, each of which is unitary and represents a cycle.

In order to evaluate the number of simple chains and cycles in a net, we define the *diagonal submatrices* of a matrix as those formed by taking some rows and the corresponding columns from it. From Theorem 1 follows immediately

THEOREM 3. *The number of simple chains including all cycles in a net is equal to the number of unitary diagonal submatrices of the connection matrix of the net.*

In practical calculation for some special cases we formulate the simple chains and cycles in another way. Regarding $||i\ j||$ as i substituted by j, we get a two-row notation of a *substitution* or *permutation* for a simple chain of order m, $\begin{pmatrix} i_1, i_2, \cdots, i_m \\ j_1, j_2, \cdots, j_m \end{pmatrix}$, where i_e is substituted by j_e. We often employ the one-row notation of cycles so that each substitution can be decomposed into several disconnected cycles. (See Dickson 1930, p. 139). Conversely every substitution of order m of subscript-pairs $||i\ j|| \neq 0$ gives a simple chain of order m.

LEMMA 1. *Each non-zero term of the determinant of a diagonal* m-*row square submatrix of* D *gives a simple chain of order* m *in* N.

Because in every non-zero term of such a determinent D_m, which is the product of m factors, +1 or —1 formed by taking one and only one element from each row and each column of D_m, all subscript-pairs of these factors form a substitution.

LEMMA 2. *The determinant* |D| *has at most*

$$a_n = (n-1)\left((n-1)! - e_{n-1}^{\,n-2}\right) \tag{2}$$

non-zero terms, where e_m^k *is determined by successive deduction from the formula*

$$e_m^k = (m-1)! + (k-1)\,e_{m-1}^{\,k-2} + (m-k)\,e_{m-1}^{\,k-1} \tag{3}$$

for $k \leqq m$ *and* $k > 2$ *with* $e_m^0 = 0$, $e_m^1 = (m-1)!$, $e_m^2 = (m-1)! + (m-2)\,e_m^1$.

We consider first a determinant D_m of order m in which k diagonal elements are zero and all other elements are non-zero. Let e_m^k be the number of zero-terms in the expansion of D_m. By successive interchanges of rows and columns we see first that e_m^k is independent of the distribution of those zeros in the diagonal line and that any determinant having but k zero-elements, of which no two lie in the same row or the same column, has exactly e_m^k zero-terms in its expansion. Formula (3) is thus easily derived by induction from D_m with zero-elements in simple arrangement. Consequently the determinant $|D|$ has non-zero terms in a number not more than

$$a_n = n! - e_n{}^n = n! - (n-1)! - (n-1)e_{n-1}{}^{n-2}$$
$$= (n-1)((n-1)! - e_{n-1}{}^{n-2}).$$

From these lemmas follows immediately

THEOREM 4. *The net* N *has at most* a_n *simple chains of order* n, *where* a_n *is determined by* (2).

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A MATHEMATICAL STUDY OF ORGANISM GROWTH AS AN APPROACH TO THE CANCER PROBLEM

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A mathematical expression is described giving the growth rate of a tissue region as a function of the determining biological factors. It is observed that within the limitations of prediction of this expression, a change of growth to the neoplastic type can be expected under certain conditions of the variables. The growth equations used here are different from others usually mentioned in that they attend to both the positive and the negative growth phases occurring in the course of organism development. The expression derived enables the prediction of an increase in incidence of cancer with age, predicts a decrease in the rate of tumor growth with increasing age, and permits an hypothesis to be made as to the nature of the action of carcinogenic agencies.

The study of growth may be approached on a number of different levels as far as environmental (both internal and external) influences upon the hereditary substrate are concerned. The most primitive of these environments concerns itself with growth and differentiation (Little, 1947). This is the environment which our mathematical treatment will consider. Another environmental phase of great importance in the cancer problem, which might also be mentioned, is that of the phenomena controlled primarily by horomones. This study of the environment concerned with growth and differentiation will be limited to the period from the time of birth to the death of the organism as this is seen in the higher animals.

In this exposition cell number will be used as the parameter representing growth. There is considerable justification for this (Shock and Morales, 1942). The idea of growth is certainly very closely bound to the tumor problem. In fact, J. Ewing (1940) states, "A tumor is an autonomous new growth of tissue." Speaking more directly, the use of cell number here as a growth parameter appears natural, since microscopically rapidity of growth in tumors is shown by evidence of *cell* division (Barnard and Robb-Smith, 1945). It should be understood, of course, that an increased rate of cell division is not actually the primary factor in tumor formation, for if it were (Berill, 1943), as cell division continued tumor cells should get progressively smaller and disappear. It appears that the increased rate of cell division is a device to insure mechanical stability as the bulk of protoplasm is increased. Using certain assumptions, N. Rashevsky (1938) showed that from physical considerations a cell above a certain size is mechanically unstable. It might be pertinent to mention here that the complete solution of the growth problem demands consideration of changes in: (1) cell size, (2) cell number, and (3) intercellular substance. The most readily observed and measured change in tumors is that of cell number. Our primary purpose here is not a complete solution of the growth problem. Our interest is centered in that phase of growth which will best enable us to study tumors.

In this discussion a tissue region will be defined as the whole of those cells of the same histological type in continuity with each other in the same organ (or organs). The total number of tissue regions in the entire body will be designated as m tissue regions and the typical tissue region will be known as the ith tissue region. The number of cells in the ith tissue will be denoted by n_i.

Let $n =$ the total number of cells in the entire organism.

Then we obtain

$$n = \sum_{i=1}^{m} n_i . \tag{1}$$

We shall define a constant g which will be used as a measure of the hereditary constitution of an organism insofar as this constitution influences change in cell number occurring in the growth process. Then the amount of g in each cell of a given individual organism is the same as that in every other cell in that organism, since the specific hereditary materials of the individual are possessed equally by all of the cells of that individual (Newman, 1932).

It is known that when groups of cells of various tissue types are placed in tissue culture medium with all exogeneous influences removed, the most significant distinguishing characteristic between these types is the difference in their rates of cell division (Fischer, 1946). This is true even though the characteristics of these cells from the point of view of genetics may have been the same, i.e., each group of cells came from the same organism. Therefore, we introduce a quantity a_i which will bear a constant value in any particular tissue region i. The numerical value of a_i will bear an inverse relation to the degree of differentiation which the ith tissue region has undergone. Then a_i will describe the influence of differentiation on cell division rates.

Let

$$G_i = a_i g , \tag{2}$$

for a single cell of type i.

The second basic quantity to be discussed is related to the concept of the individuation field in experimental embryology. It must be remembered that most of our knowledge about the individuation field deals with what in the higher animals is the prenatal stage of growth, but that in this particular discussion, however, we limit ourselves to the post-natal stage. The existence of this field is a consequence of cellular aggregation in metazoans. Body development is not a product of the cell but of other much more general formative forces. In tissue culture it has been shown that changes which the cell undergoes from maturity to death—growth, differentiation, and function—are not changes peculiar to it, but merely a reaction which it may suffer under the influence of different conditions in its environment (Burrows, Jorstad, and Ernst, 1926). A number of examples of interactive effects are: (1) competition of cells for nutrient substances, (2) mechanical effects (compression), (3) spatial effects, such as distortion of nutritive diffusion fields of a cell by its neighbors, (4) production of harmful metabolites, (5) growth-stimulating agents, (6) the influence of specialized functions, (7) organization, and (8) accumulation of products which are not dissolved out under the condition of organization found normally in the body of the organism. We will use the symbol J_i to represent the effect of such interactive influences on cell division rates in the ith tissue region.

The quantities G_i and J_i will be assumed to have additive properties so that we can let

$$\frac{dn_i}{dt} = n_i G_i - J_i, \tag{3}$$

where t is taken as time and where G_i is multiplied by n_i, since we are dealing with a tissue region of n_i cells.

The quantity J_i is a function of time, and by the accumulation of J_i, when cells aggregate in sufficiently large numbers, their growth is gradually slowed down and may eventually be given a negative value. The quantity J_i is usually an increasing function of age. Anatomically such increase might be said to be observable in the decrease in cellular elements and with the increase in intercellular substance coming with age. Changes in tissue fluids with aging of the metazoan body are inevitable. They are probably of many kinds and result sooner or later in alterations in the cells subjected to them. The cells fail to function as they should and the whole cellular community may be invalidated or die as a result (Cowdry, 1942). The same idea is made manifest by the work of A. Carrel and M. T. Burrows (1911), who found that plasma was not an optimum medium for the growth of cells planted in it. When diluted by two volumes of distilled water to three volumes of plasma, much better results were secured. In our language this would be a decrease of J_i. In tissue culture where environment is frequently changed, there is no opportunity for J_i to increase (accumulate), and cells can and do grow indefinitely. Cells in tissue culture demonstrate very many of the properties of neoplasia. In the case of unicellular organisms and in metazoans of small size like hydra and planaria, gross aggregation of cells with resultant irreversible increase (accumulation) of J_i is not present, and such organisms achieve a kind of immortality (Heilbrunn, 1943).

A certain minimum value of J_i (or interactive effect among cells) seems necessary for any growth to occur at all since, when individual cells or small groups of cells are brought into media where nutritive requirements are satisfied, growth will not occur unless a certain minimum number of cells is present (Fischer, 1946).

Let ν_i be the minimum number of cells of type i which must be together in aggregation for any cell division to occur at all. When $n_i < \nu_i$, no cell division occurs. When $n_i = \nu_i$, $dn_i/dt = 0$. When $n_i > \nu_i$, $dn_i/dt > 0$.

We will assume that

$$J_i = f(n, n_i, t). \tag{4}$$

We are making J_i an explicit function of t, which is a departure from previous equations of this type (Rashevsky, 1945). In so doing, we recall our previous remarks on the changes of intercellular substance and of tissue fluid occurring with age. In the final integrated equation which gives n_i as a function of t, this will permit n_i to reach a maximum and then decrease as the process of senescence sets in. In other equations which have been used heretofore, n_i approaches a limiting maximum value with age. N. Rashevsky has pointed out the objectionability of the anthropopsychic concept inherent in the use of time in this way, which assumes that the organism knows its own time or carries its own clock. More desirable than the use of time in our equations might be the use of change in entropy due to physiological activity of the organism under discussion. Assuming J_i to be an increasing function of entropy would result in some interesting theoretical possibilities. The increase in entropy accompanying the course of physical experience is only probable and never certain. In the statistical interpretation of the second law of thermodynamics there is always a probability that any given state will occur if one waits long enough. We are not prepared to say at present whether this is wholly comparable to the device to be used in equation (43).

Since each cell of the organism interacts with each cell of tissue region i by an average amount, we can put $J_i = ntf''(n_i)$.

Reasoning that the J_i for n_i cells is approximately n_i times what it is for one cell when n_i is large, and remembering that when $n_i = \nu_i$, $dn_i/dt = 0$ and when $n_i > \nu_i$, $dn_i/dt > 0$, we let

$$J_i = b_i t n (n_i - \nu_i) + \nu_i G_i , \tag{5}$$

introducing the constant b_i defined for the ith tissue region. Tentatively, the simplest biological concept which may be attached to b_i is that of organization. Groups of cells of similar structure and performing similar specialized functions are called tissues. A further specialization or *organization* of the various tissues into organs is met within the higher forms. Each organ consists of several kinds of tissues built into a structural and functional unit (Carlson and Johnson, 1941).

Substituting equation (5) into (3) we find:

$$dn_i/dt = n_i G_i - b_i t n (n_i - \nu_i) - \nu_i G_i . \tag{6}$$

In a tissue culture $n = n_i$ and b_i would be far smaller in numerical value than in the organized body. In tissue culture we let $b_i = b_{it}$. Therefore,

$$dn_i/dt = n_i G_i - b_{it} n_i t (n_i - \nu_i) - \nu_i G_i . \tag{7}$$

By adding up the growth rates of individual tissue regions we may obtain the growth rate of the body as a whole. Define the quantities G, b, ν, and n by

$$G = \frac{\sum_{i=1}^{m} G_i}{m}, \qquad b = \frac{\sum_{i=1}^{m} b_i}{m}, \tag{8}$$

$$\nu = \sum_{i=1}^{m} \nu_i , \qquad \text{and} \qquad n = \sum_{i=1}^{m} n_i . \tag{9}$$

Then from equations (1) and (6) we obtain:

$$dn/dt = nG - btn(n - \nu) - \nu G . \tag{10}$$

Unfortunately, there appears to be no other way except by using a power series to obtain an exact solution of equation (10). However, a solution of (10) is readily available if we simplify it to the form

$$dn/dt = nG - btn^2 . \tag{11}$$

This may be at least partially justified by noting that $n >> \nu$ while only $n_i > \nu_i$.

The choice of a point for making $t = 0$ poses a problem. Here we choose birth as this point. Our reasons are perhaps not totally adequate, but include: (1) the peculiar intimacy of contact of foetal (and embryonic) tissues with the exterior through the medium of the placenta, whose permeability characteristics as a stimulus to growth might be such as to drain off accumulated J_i, the destruction of this relationship producing a biological discontinuity at birth; (2) the small size of the organism during its prenatal period with resultant decreased irreversible increase of J_i; (3) the use of conception as a zero point for time would make little practical difference, since early in the organism's existence J_i is small; (4) it is only with difficulty that the present theory can be used for prenatal development, since in such development the a_i's for the different tissue regions would certainly be variables rather than constants, as we have assumed them to be in post-natal life; and (5) prenatal life-span is very small compared to post-natal life-span.

In general it should be observed that equation (11) is less descriptive of reality in the first few years of life than at other times. Assuming that at birth $t = 0$, equation (11) would give a very high dn/dt (or growth rate) at the birth of the individual, with dn/dt at birth as great as that seen in tissue culture growth. It is known, however, that growth is very rapid in the early years of life.

The solution of equation (11) is found to be

$$n = G^2/[b(Gt - 1) + ce^{-Gt}], \qquad (12)$$

where c is an integration constant.

Taking the partial derivative of n with respect to t in equation (12), we find:

$$\partial n/\partial t = -[G^2 b(Gt - 1) + ce^{-Gt}]^2 [bG - cG^{-Gt}], \qquad (13)$$

$$bG - cGe^{-Gt_m} = 0 \text{ for the maximum } n, \qquad (14)$$

$$t_m = \frac{\log(c/b)}{G}. \qquad (15)$$

The maximum number of body cells is then

$$n_m = G^2/(b \log[c/b]). \qquad (16)$$

The number of cells in the body at birth is found by making $t = 0$ in equation (12). This gives:

$$n_b = G^2/(c - b). \qquad (17)$$

The t given in equation (15) is probably about 20 years, since this is the age when maturity is said to be first reached (Scammon, 1942).

An interesting surmise suggested by equation (12) is that at the age which might be the absolute limit of the possible human life-span under optimal circumstances, there are about the same number of cells in the body as at birth. In senescence there are known to be many similarities to a youthful condition. L. V. Heilbrunn (1943) gives 110 years as about the longest authenticated life-span. We will take 150 years as being the limit of the human life-span (Bogomolets, 1946).

When

$$t = 20\,, \quad n = 3.55 \times 10^{13} \quad \text{(Arey, 1946)}. \tag{18}$$

When

$$t = 20\,, \quad dn/dt = 0\,; \tag{19}$$

$$n_{t=0} = n_{t=150}\,; \tag{20}$$

$$dn/dt = Gn - btn^2\,; \tag{21}$$

$$0 = G(3.55 \times 10^{13}) - 20b(3.55 \times 10^{13})^2\,; \tag{22}$$

$$G/b = 7.10 \times 10^{14}\,. \tag{23}$$

From equations (15) and (19), we find:

$$20G = \log(c/b)\,, \tag{24}$$

and from equations (12) and (20), we find:

$$-b + c = 150bG - b + ce^{-150G}\,. \tag{25}$$

From equation (24) we get:

$$b/c = e^{-20G}\,. \tag{26}$$

Equation (25) gives us

$$1 = 150\frac{bG}{c} + e^{-150G}. \tag{27}$$

Using equation (26) we obtain:

$$1 = 150Ge^{-20G} + e^{-150G}\,. \tag{28}$$

Multiplying both sides of this equation by e^{20G}, we find:

$$e^{20G} - e^{-130G} = 150G\,; \tag{29}$$

Solving equation (29) graphically, we find:

$$G = 0.158\,. \tag{30}$$

From equation (23), we obtain:

$$b = G/(7.10 \times 10^{14}), \tag{31}$$

$$b = 0.0223 \times 10^{14} \,. \tag{32}$$

Let

$$c = \gamma \times 10^{-14} \,. \tag{33}$$

Introducing equation (18) in (12), we find:

$$\begin{aligned} 3.55 \times 10^{13} = {} & (0.158)^2/[0.0223 \times 10^{-14}(0.158 \times 20 - 1) \\ & + (\gamma \times 10^{-14})(e^{-0.158 \times 20})] \\ \gamma = {} & 0.522 \\ c = {} & 0.522 \times 10^{-14} \,. \end{aligned} \tag{34}$$

Because of simplifying assumptions, the numerical values given G, b, and c are orders of magnitude only.

Using the values obtained for G, b, and c in equation (12), we obtain:

$$n = \frac{(0.158)^2}{0.0223 \times 10^{-14}(0.158t - 1) + 0.522 \times 10^{-14} e^{-0.158t}} \,. \tag{35}$$

The graph of equation (35) appears in Figure 1.

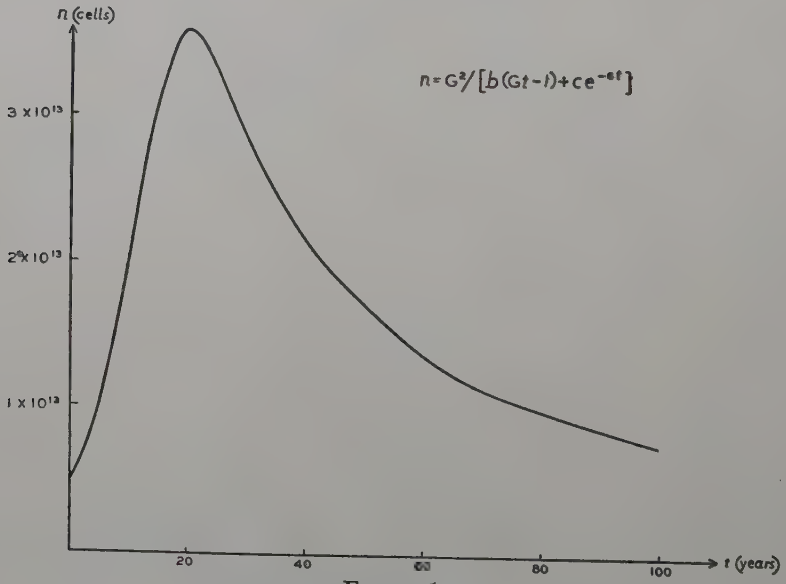

FIGURE 1

Remembering equation (2), we will define

$$a = G/g \,. \tag{36}$$

Then

$$G = ag \, . \tag{37}$$

Substituting equation (2) into (7) and equation (37) into (12), and then substituting equation (12) into (7), we obtain

$$\frac{dn_i}{dt} = n_i a_i g - \frac{b_i t a^2 g^2 (n_i - \nu_i)}{b(agt-1) + ce^{-agt}} - \nu_i a_i g \, , \tag{38}$$

$$\begin{aligned} \frac{dn_i}{dt} + \left[\frac{b_i t a^2 g^2}{b(agt-1) + ce^{-agt}} - a_i g \right] n_i & \\ = \frac{b_i t a^2 g^2 \nu_i}{b(agt-1) + ce^{-agt}} - \nu_i a_i g \, . & \end{aligned} \tag{39}$$

Equation (39) is a linear differential equation of the first order with the following solution:

$$\begin{aligned} n_i = \exp & \left\{ - \int \left[\frac{b_i a^2 g^2 t}{b(agt-1) + ce^{-agt}} - a_i g \right] dt \right\} \\ \int \Bigg[\exp & \left\{ \int \left[\frac{b_i a^2 g^2 t}{b(agt-1) + ce^{-agt}} - a_i g \right] dt \right\} \\ & \frac{b_i t a^2 g^2 \nu_i}{b(agt-1) + ce^{-agt}} - \nu_i a_i g \Bigg] dt \\ + c_i \exp & \left\{ - \int \left[\frac{b_i t a^2 g^2}{b(agt-1) + ce^{-agt}} - a_i g \right] dt \right\} \end{aligned} \tag{40}$$

with c_i the integration constant. Since the integrals in equation (40) can not be evaluated readily, a graphical integration will probably be necessary.

Qualitatively from the conditions of the derivation of equation (40) we can take a guess at the form of the graph of n_i plotted against t. There will be an increase in youth and then a decline of n_i will set in with increasing age. However, in certain regions, dependent on the values of a_i, b_i, and ν_i, a release of an adequate number of cells from intercellular controls will be effected at some age with resultant sudden cellular proliferation occurring which will fit the description of neoplastic growth.

The cancer problem is being attacked today by a multiplicity of methods which are rather diverse in approach and viewpoint. We will make an attempt here to show how some of these may be fitted into our theoretical study.

It is known that in the process of growth and cell division a very small number of cells will occur, say two or three in tens of thousands, which will have a heredity different from their ancestors. We are not speaking here of the small, continuous, accidental variations that are bound to occur even in the most homogeneous population, which variations are not heritable and in our theory may be accounted for through the characteristics of b_i. We are speaking of heritable changes where a discontinuity manifests itself because there are no intermediate forms between the unchanged and the few changed. The biologist calls these discontinuous changes mutations. We will interpret these mutations as changes in g which may occur spontaneously in any body cell and changes which the offspring of that body cell will possess. These changes are truly spontaneous and intrinsic for, as E. Schrödinger (1945) shows, thermal agitation, which is always present at the temperature at which living substance is maintained, is able to account for these spontaneous mutations.

The cancer viruses (Rous, 1935-1936) and the "milk factor" (Bittner, 1942), which is probably of a nature similar to that of cancer viruses, add a degree of complexity. We shall count cancer virus as a contributor to g. J. Needham (1942) makes the observation that the objection to the virus theory of cancer lies in the fact that it primarily emphasizes the exogenous origin of uncontrolled specific proliferation. He wonders whether the difference between transmissable and non-transmissable tumors may not be any more mysterious than the capacity which some enzyme systems possess and others do not, of coming out into cell-free extracts of tissues. Malignancy (Berill, 1943) may be one of the many properties of a cell induced in host cells by its non-cellular extracts. Similar extracts of non-malignant cells might have similar induction properties, but without simultaneous conveyance of malignancy and consequent growth they remain undetected. There are many properties which the gene and virus possess in common and the possibility must exist of the virus being a sort of gene-like body which can survive transmission through a cell-free extract and which once becoming part of the cellular mechanism remains that (Fischer, 1946). Of interest in this direction is that transmission by cell-free filtrates of fowl tumors induced by tar has been reported (McIntosh and Selbie, 1939).

One of the ideas pertinent to neoplasm formation is that a tumor represents an escape of cells from a combination of injurious agents which would otherwise eventually cause death of the cell. The escape is accomplished by the acquisition of a new form of metabolism by the cell which cannot be adversely affected by the injurious agents

(Moore, 1944). This may be a means by which such a large number of cells are born and killed that the probability of a single cell coming into existence with a mutation bringing a sudden increase in g is vastly increased. This mutant will have abnormal hereditary tendencies and altered structures. The new metabolic process in the cells is neither normal nor subject to the usual restraints, and the growth and multiplication of the cells proceeds autonomously. The assumption of a higher glycolytic coefficient may be one of the alterations and one which has been shown (Rashevsky, 1940) adequate to produce many of the characteristics of neoplastic growth and cell division.

Considering g further, we will mention the growth-promoting abilities of embryo extract; as well as of tumor cell extracts. Allied with it is the observation that rapidly growing embryonic tissues frequently show pyknotic nuclei and degenerating cells (Needham, 1942). It seems that cells have extractable products, which also appear on cellular degeneration, and have the power to increase what we call the value of g assigned to the cell.

Our J_i is related to the concept of the individuation field in experimental embryology. Cancerous growth is an escape from the controlling pattern or field.

S. Bayne-Jones et al. (1937) have asked the very important question, "Have they [malignant cells] become 'fast' to the conditions which normally control cell growth in the body, or is there a break in the internal control mechanism of the cell, or is there a loss in body control of cell activity? This, the core of the problem, has been almost entirely neglected." We propose to show that all these processes together are operative in the production of the cancer cell.

According to equation (3) positive growth, of a neoplastic type or otherwise, will occur only when

$$n_i G_i > J_i \,. \tag{41}$$

To satisfy equation (41) we must either increase $n_i G_i$ (which is equal to $n_i a_i g$, by definition of G_i), or decrease J_i, or do both. We will describe cases of each of these theoretically predicted methods of carcinogenesis as demonstrated in the experimental laboratory.

An increase in the $n_i a_i g$ term is most significantly due to a change in g. Such an increase in g has been demonstrated in the neoplastic transformation of normal cells grown in tissue culture. In the work of A. Nettleship and W. R. Earle (1943) mouse fibroblasts were treated in tissue culture with methylcholanthrene. Cultures of such cells, when transplanted subcutaneously into the same strain of mice from which they were derived, grew there with all the characteristics generally ascribed to cancerous tissue and eventually caused the death of their hosts. That the change was in $n_i a_i g$ is evidenced by the fact that in the tissue into which the cells were transplanted there was obviously approximately the same value for J_i as in the tissue from which the cells were originally extirpated.

In illustrating the affects of decreased J_i we turn to the results of A. Fischer (1937), who by transplanting pieces of various tissues into abnormal sites in the same animal from which the pieces of tissue were removed, was able to produce neoplasms from this transplanted tissue. Apparently the inhibition (measured by J_i) to the proliferation of the cells which was exerted in their normal sites was not so great in some of the new locations into which they were transplanted and, therefore, the size of the value of $n_i a_i g$ which remained constant was sufficiently great to cause a rapid growth in the new sites.

As a case of an elevation of $n_i a_i g$ and a depression of $J_i (= b_i tn [n_i - \nu_i] - \nu_i G_i)$ occurring simultaneously, reference may be made to the work of K. Yamagiwa and K. Ichikawa (1918), in which epidermoid carcinoma developed on the ears of rabbits painted with coal tar. Regarding the effect of tar on J_i, it is known that under certain conditions methylcholanthrene can be a destroyer of tissue, and can cause cell death (Earle and Voegtlin, 1938). With this cell destruction there would be a decrease in n_i and perhaps also a decrease of b_i, with resultant decrease of J_i. With random cell death those cells surviving might absorb some of the diffusable products of their dead neighbors, with other changes in g of the cells of the tissue occurring by mechanisms described previously as means of elevating g in a cell. There is a vast variety of substances which have been shown to be carcinogenic and which are certainly very diversified in nature. J. P. Greenstein (1947) mentions, too, bakelite discs, zinc salts, x-radiation, ultra-violet radiation, phthalate buffer in HCl, estrogens, cysticercus, etc., as carcinogenic agents. The simplest generalization which might be drawn from this is that any agent which may be applied over a prolonged period of time and which causes a selective necrotizing process of cells but spares some cells may cause those cells surviving to undergo malignant change. In this connection it might be interesting to mention the action of benzol on bone marrow (Goodman and Gilman, 1941). Benzol, because of its destructive effects on bone marrow cells, has previously been used in the treatment of the lukemias (tumors of bone marrow). Paradoxically, chronic benzol poisoning has produced lukemia as an end result. Likewise, x-rays are one of the accepted treatments for cancer, yet it is well known that exposure to x-radiation can produce cancer in a previously healthy tissue. This same idea may be extended to many other carcinogenic agents.

The influence of age on the rate of growth of a tumor is well known, with tumors in early life tending to progress much more rapidly than do the same tumors in later life. Assuming all other quantities are the same, this may readily be seen from:

$$dn_i/dt = n_i G_i - b_i tn(n_i - \nu_i) - \nu_i G_i\,,$$

which gives the rate of growth of a tissue region (dn_i/dt), no matter what be the cause of the growth, as a function of age (t). This equation under other conditions can predict the falling off of the wound-healing rate with increasing age.

The incidence of cancer seems to be an increasing function of age despite the inaccuracies inherent in our present statistics. Following the approach of N. Rashevsky (1945), we will show how the theory may account for this increased probability of occurrence. Using equations (41) and (5) we see that for growth to occur at all we must have

$$n_i G_i > [b_i tn(n_i - \nu_i) + \nu_i G_i]\,.$$

It follows that

$$n_i G_i + \nu_i G_i > b_i tn(n_i - \nu_i),$$

$$\frac{n_i G_i + \nu_i G_i}{n_i - \nu_i} > b_i tn\,,$$

and

$$b_i < \frac{G_i}{tn}\left(\frac{n_i + \nu_i}{n_i - \nu_i}\right). \tag{42}$$

It is known by the statistical treatment of nearly all fluctuating characters that among the members of any large group of organisms we obtain the form of the normal curve of probability (Woodruff, 1941). Of the different quantities used in our equations that vary significantly among the different members of a species, we have g and b_i. At present we might suppose that g varies in the discontinuous way which hereditable variations do. Quantity b_i will be considered as one of those fluctuating continuous variations which has an average value in the species of $\bar{b}_i$ and where the probability of b_i in a particular individual deviating from $\bar{b}_i$ by an amount $(\bar{b}_i - b_i)$ is given by

$$N(\bar{b}_i - b_i) = Ae^{-\sigma(\bar{b}_i - b_i)^2}\,. \tag{43}$$

We get the probability $W_i(t)$ of a cancer occurring in the ith tissue region of an individual at a given age from the following equation by substituting equation (42) into (43), giving us

$$W_i(t) = Ae^{-\sigma\left[b_i - \frac{G_i}{tn}\left(\frac{n_i + \nu_i}{n_i - \nu_i}\right)\right]^2} . \qquad (44)$$

It can be seen that $W_i(t)$ will increase with age, since

$$\frac{G_i}{tn}\left(\frac{n_i + \nu_i}{n_i - \nu_i}\right)$$

is an increasing function of age. In the numerator we only have n_i decreasing with age, while in the denominator we have $(n_i - \nu_i)$ getting very small with age, with a decreasing n and a t increasing relatively slowly compared to the decrease of $(n_i - \nu_i)$.

Grateful acknowledgment is made to Professor N. Rashevsky for his inspiration and invaluable counsel, and also to Dr. Anatol Rapoport for his helpful suggestions and criticisms during the preparation of this paper.

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ADDENDUM

According to W. R. Earle (personal communication dated April 2, 1948), it has been possible to grow the single cell of one cell type in tissue culture, with the difficulty in accomplishing this probably due to the unsatisfactory nature of the culture medium used in tissue culture.

This recent accomplishment would not seem to make untenable our concept of ν_i as the minimum number of cells of type i which must be together in aggregation when any cell division will occur at all, insofar as the intact organism is concerned. Growth rate in tissue culture is usually more rapid than that seen in the organism *in vivo.* The body fluids would then not seem as satisfactory (for furnishing media for positive cell growth) as some of the artificial fluids used.

In previous tissue culture growth experiments, single cells could not be grown, with a minimum number of cells required for growth to occur at all. Reasoning from these facts, it would seem that *in vivo* a larger group of tissue cells would be required to initiate a positive growth change.

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CAN ELASTIC STRESSES IN GELS CAUSE THE ELONGATION AND DIVISION OF A CELL?

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Some metabolites present in the cell may affect its colloidal structure. If the cytoplasm is in the state of a gel, elastic stresses may appear as a result of non-uniform concentration of some metabolites which affect mechanical properties of gels. This paper investigates the question whether mechanical stresses, thus produced, can result in such a deformation of the cell which may lead to a division. The result of this study indicates that this is not possible. Elastic stresses, produced by non-uniformities of concentration of metabolites which affect the colloidal structures of the cytoplasm, may produce only a general dilation or contraction of the system, without change in shape.

The success of the diffusion forces theory of cell division (Rashevsky, 1940, 1948; Landahl, 1942) in predicting with accuracy the time course of the elongation and constriction of freely dividing demembranated *Arbacia* eggs (Buchsbaum and Williamson, 1943) has led to a certain neglect in the study of other possible causes of cell division. The only other quantitatively treated possibilities were those of variable surface tension (Rashevsky, 1931, 1938; Shimbel, 1946), and the purely formal approach based on the principle of maximum energy exchange (Rashevsky, 1943; Stanton, 1944).

While these approaches also lead to a mathematical description of the dynamics of elongation, they do not directly give us any indication as to the order of magnitude of the quantities involved. In that respect the diffusion force theory has a definite advantage. (Rashevsky, 1938; 1940).

Because the diffusion force theory gives us only the description of the overall process of the division of a cell as a whole, and is inadequate for the description of the phenomena of nuclear division (Rashevsky, 1938; Schrader, 1944), all other possibilities should be studied mathematically in a systematic way.

The protoplasm is a complex colloidal system which may undergo various sol-gel transformations. Substances dissolved in a gel in general may cause phenomena of hydration, or other phenomena which result in the change of the specific volume of the gel. Non-uniformities of the concentrations of a dissolved substance may thus produce non-uniformities in expansion or contraction of a gel, thus causing mechanical stresses. The question arises whether such mechanical stresses may produce an overall elongation of a cell with a resulting division. The question becomes of special interest because the biological importance of mechanical stresses in gels has been emphasized in the field of embryology (Weiss, 1934; 1940).

The presence of protoplasmic streamings during cell division would seem to indicate its fluidity and any assumption of stresses may appear absurd. The question is nevertheless worth studying, because the protoplasm is known to sometimes possess both the properties of an elastic solid, and of a viscous liquid.

In developing a mathematical theory of such a contradictory physicochemical system, we will have to use somewhat contradictory methods. In computing the stresses, we shall consider the system as a solid. From the stresses, we shall compute the volume and surface forces acting on the system. Then we shall assume that under the prolonged effect of such forces, the system behaves as a plastic body, and thus compute its rate of deformation.

Let the specific volume of an element of our system be V_0 in the absence of any dissolved substances. Let a substance be present in non-uniform concentration $c(x, y, z)$, and let that substance cause a dilation of the system. If α denotes a constant and $\phi(c)$ any arbitrary continuous function of c, then the linear expansion may be represented by $1 + \alpha\,\phi(c)$, and the volume V_0 changes to $V_0[1 + 3\,\alpha\,\phi(c)]$. The problem of computing the stresses due to such an expression is formally identical with the problem of computing thermal stresses in a solid with a coefficient of linear thermal expansion α in a non-uniform field of temperature ϕ. Denote by E the modulus of elasticity and by σ the Poisson ratio. The elastic stresses and strains in such a system are the same (Timoshenko, 1934) as produced by a system of volume forces F:

$$F = -\operatorname{grad}\frac{\alpha E \phi}{1-2\sigma} = \operatorname{grad}\Phi; \qquad \Phi = -\frac{\alpha E \phi}{1-2\sigma}; \tag{1}$$

per unit volume, and by a system of normal surface forces

$$F_s = \frac{\alpha E \phi}{1-2\sigma} = -\Phi; \tag{2}$$

the outward direction of the normal being taken as positive.

We now ask the question: if the forces (1) and (2) affect a plastic body of viscosity η what will the *average* rate of plastic flow in a given direction be?

To answer that question, we may use Betti's theorem, as has been done before (Rashevsky, 1940; 1948). It must, however, be noted, that whereas before we considered the plastic body as incompressible, and therefore set $\sigma = \frac{1}{2}$, we cannot do that now. In fact, putting $\sigma = \frac{1}{2}$ will make both forces (1) and (2) infinite, which is rather obvious physically. Hence, we must use Betti's theorem in its most general form. Denoting the overall length of the system in the z-direction by l_z, by V—the total volume of the system—by X, Y, Z, and X_ν, Y_ν, Z_ν the components of F and F_s respectively, we now have:

$$\frac{1}{l_z}\frac{d\,l_z}{dt} = \frac{1}{3\,\eta\,V}\left\{\iiint\limits_V [zZ - \sigma(yY + xX)]\,dV + \iint\limits_S [zZ_\nu - \sigma(yY_\nu + xX_\nu)]\,dS\right\}. \tag{3}$$

Even though $F = \operatorname{grad}\Phi$, the volume integral now cannot be transformed completely into a surface integral, as is the case for $\sigma = \frac{1}{2}$ (Young, 1939).

Integrating by part the first term of the volume integral in (3) we find now

$$\iiint z\frac{\partial\Phi}{\partial z}\,dV = \iint\limits_S \Phi\, z\cos(\nu, z)\,dS - \iiint\limits_V \Phi\,dV. \tag{4}$$

Similar expressions are obtained for the other two terms. The whole volume integral now becomes equal to

$$\iint\limits_S \Phi\{z\cos(\nu, z) - \sigma[y\cos(\nu, y) + x\cos(\nu, x)]\}\,dS - (1 - 2\,\sigma)\iiint\limits_V \Phi\,dV. \tag{5}$$

From equation (2) it follows that

$$X_\nu = F_s\cos(\nu, x) = -\Phi\cos(\nu, x), \text{ etc.} \tag{6}$$

Introducing expressions (5) and (6) into equation (3) we find that the two surface integrals cancel each other out and thus, because of equation (2), we obtain:

$$\frac{1}{l_z}\frac{d\,l_z}{dt} = -\frac{1}{3\,\eta\,V}\iiint\limits_V \Phi\,dV = \frac{\alpha E}{3\,\eta\,V(1 - 2\,\sigma)}\iiint\limits_V \Phi\,dV. \tag{7}$$

Exactly the same expressions are obtained for $(1/l_x)(dl_x/dt)$ and $(1/l_y)(dl_y/dt)$. Hence, the shape of the body remains unchanged. For $\phi > 0$ an average dilation occurs, for $\phi < 0$—an average compression. No overall change in shape, such as an elongation and constriction will occur in this case.

It may be argued that this negative result is due to the contradictory assumptions made about the simultaneous behavior of the system as an elastic solid and a plastic fluid. But the negative result holds *a fortiori* if we make more rigorous assumptions. If the system behaves only as an elastic body, no plastic flow is possible. By now applying Betti's theorem to calculate the *average* elastic strains, we find again that only an average constant dilation or compression remains. If, on the other hand, the system is a purely plastic body, no stresses are possible, and hence no forces due to stresses.

It must be kept in mind, however, that Betti's theorem gives only the *average rate of plastic deformation* in a given direction, or, for an elastic system, only the *average strain* in that direction. From the fact that these average values are zero or the same in all directions, it does not follow that the same theorem holds for every element of volume of the system. The system of forces (1) and (2) may in general produce internal plastic flows, leaving the overall shape of the body invariant. The calculation of these *local* flows is, however, a problem of an entirely different order of mathematical difficulty. It is quite possible that such internal local displacements may play a role in such cases of mitosis which leave the cell as a whole undeformed.

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ON THE EFFECTS OF A CONSTANT SUB-THRESHOLD CONDITIONING STIMULUS UPON THE RESPONSE TO A CONSTANT CURRENT TEST STIMULUS

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The strength of a test stimulus, which is just adequate to produce a response after a sub-threshold conditioning stimulus, is calculated on the basis of Rashevsky's two-factor theory as a function of the strength and duration of the conditioning stimulus. The results are compared with available data for one of a family of curves and found to be in satisfactory agreement.

If a nerve is subjected to a sub-threshold stimulation, its response to a test stimulation is altered. In the present paper we shall consider, in terms of the two-factor theory of N. Rashevsky (1938), the effect of a conditioning stimulus on a cathodal test stimulation when both are constant currents. This problem has been investigated experimentally by J. Erlanger and H. S. Gasser (1937).

At the time $t = 0$ let a constant sub-threshold current $f_c R$, R being the rheobase, be applied and maintained for a time τ. At $t = \tau$ let the current be suddenly changed to $(f_c + \Delta)R$ so that Δ is the fraction of the rheobasic current added at $t = \tau$ and maintained indefinitely. We shall consider such values of Δ as are just adequate to initiate excitation at some time after $t = \tau$. Let excitation occur at a time $t = t^* + \tau$.

Following N. Rashevsky (1938), we may write the differential equations governing the excitatory state ε and the inhibitory state j in terms of the constants K, M, k and m and the initial values ε_0 and j_0:

$$\frac{d\varepsilon}{dt} = Kf_cR - k(\varepsilon - \varepsilon_0)\,, \tag{1}$$

$$\frac{dj}{dt} = Mf_cR - m(j - j_0)\,. \tag{2}$$

Since the current in the interval between zero and τ is constant, we may write for $\varepsilon(\tau)$

$$\varepsilon(\tau) = \varepsilon_0 + \frac{Kf_cR}{k}(1 - e^{-k\tau}) \tag{3}$$

and a similar expression for $j(\tau)$. For any time $t > \tau$ the current is constant, and equal to $(f_c + \Delta)R$. Hence, since $\varepsilon = \varepsilon(\tau)$ is given by equation (3), we may write, if $t' = t - \tau$,

$$\begin{aligned}\varepsilon(t > \tau) = \varepsilon_0 &+ \frac{Kf_cR}{k}(1 - e^{-k\tau})e^{-kt'} \\ &+ \frac{K(f_c + \Delta)R}{k}(1 - e^{-kt'}).\end{aligned} \tag{4}$$

A similar expression holds for $j(t > \tau)$.

Excitation occurs at the time $t' = t^*$ when $\varepsilon = j$. Hence setting $\varepsilon(t > \tau)$ of equation (4) equal to the similar expression for $j(t > \tau)$ and then introducing $t' = t^*$, we obtain an expression relating τ, t^*, f_c and Δ:

$$\begin{aligned}\varepsilon(\tau + t^*) - j(\tau + t^*) = \varepsilon_0 - j_0 &+ \frac{Kf_cR}{k}(1 - e^{-k\tau})e^{-kt^*} \\ - \frac{Mf_cR}{m}(1 - e^{-m\tau})e^{-mt^*} &+ \frac{K(f_c + \Delta)R}{k}(1 - e^{-kt^*}) \\ - \frac{M(f_c + \Delta)R}{m}(1 - e^{-mt^*}) &= 0.\end{aligned} \tag{5}$$

Since Δ is by definition the smallest value necessary for the test stimulus to produce excitation, t^* must also determine a maximum for $\varepsilon - j$. Thus for $t' = t^*$, $d[\varepsilon(\tau + t') - j(\tau + t')]/dt' = 0$. Hence we may solve for t^* and obtain

$$t^* = \frac{1}{k - m}\log\left(\frac{K}{M}\right)\left(\frac{\Delta + f_c e^{-k\tau}}{\Delta + f_c e^{-m\tau}}\right). \tag{6}$$

The cathodal rheobase, R, may be determined from the equation (Rashevsky, 1938):

$$\frac{j_0 - \varepsilon_0}{R} = \frac{K}{k}\left[1 - \left(\frac{M}{K}\right)^{k/(k-m)}\right] - \frac{M}{m}\left[1 - \left(\frac{M}{K}\right)^{m/(k-m)}\right]. \tag{7}$$

Substituting values for t^* and R from equations (6) and (7) into equation (5) we have

$$\begin{aligned}&\left(m-\frac{Mk}{K}\right)(1-f_c-\Delta)(\Delta+f_c e^{-k\tau})^{m/(k-m)}\\&=\left\{\frac{Mk}{K}\left(\frac{M}{K}\right)^{m/(k-m)}-m\left(\frac{M}{K}\right)^{k/(k-m)}\right\}\\&\times\{(\Delta+f_c e^{-m\tau})^{k/(k-m)}-(\Delta+f_c e^{-k\tau})^{m/(k-m)}\},\end{aligned}\tag{8}$$

which determines the relation between Δ and the independent variables f_c and τ in terms of three constants (M/K), k and m. If we assume that $K/k = M/m$ (normal accommodation), equation (8) reduces to

$$(\Delta+f_c e^{-m\tau})^k=(\Delta+f_c e^{-k\tau})^m,\tag{9}$$

so that $\Delta(f_c, \tau)$ is determined by the two constants k and m.

In Figure 1, Δ is plotted against τ for $f_c = -0.5$, 0.5 and 0.9, using equation (9). The dotted lines are obtained by using $k = 1160$ and $k/m = 20$. The solid line is given to illustrate the dependence upon k/m. In this case $k = 750$ and $k/m = 10$. The points are experimental values by J. Erlanger and H. S. Gasser (1937), Figure 44, page 95. The data are represented particularly well by the solid curve.

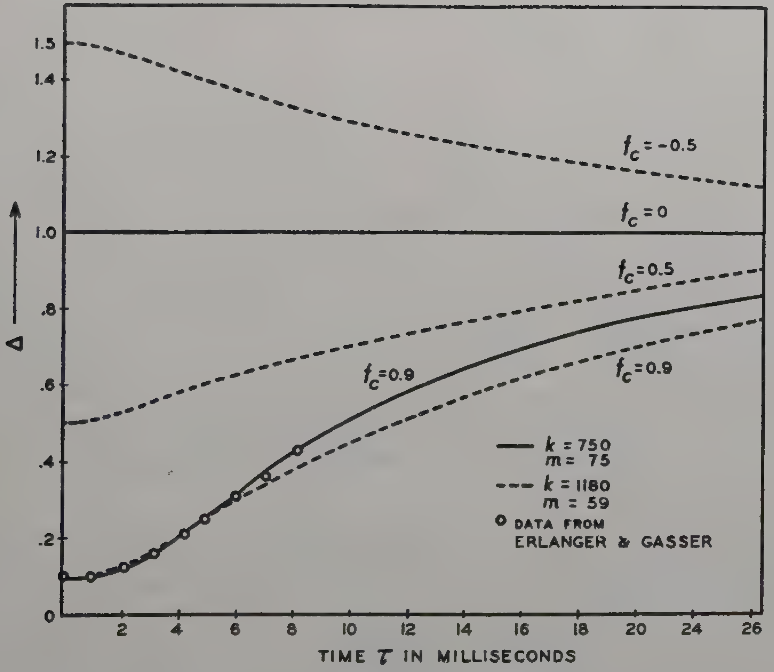

FIGURE 1

If k and m are determined independently from intensity-time data with constant current and from data with alternating current, then the curves are completely determined unless $K/k \neq M/m$.

When $K/k \neq M/m$, equation (8) must be used. From this equation it is not easy to determine Δ for given f_c and τ even if the constants are known. Define ρ and α by the equations: $\rho \equiv k/m$ and $M/m = (1 + \alpha)K/k$. If $\rho \lesssim 0.1$, $\alpha \lesssim 0.1$, and $\Delta \gtrsim 0.1$ (which holds at least if $f_c \lesssim 0.9$), then, since α^ρ is approximately equal to $1 + \rho \log \alpha$, we may write very roughly:

$$\Delta = 1 - f_c(e^{-m\tau} - \alpha)/(1 - \alpha) + \rho(1 + \alpha) \log(\Delta + f_c e^{-k\tau}). \quad (10)$$

We may take as a first approximation Δ_1 to Δ the expression given by the right-hand side of equation (10) but with the third term omitted. Then substituting this value into the right-hand side of equation (10) we have the second approximation Δ_2 to Δ

$$\begin{aligned} \Delta_2 = 1 - f_c \frac{e^{-m\tau} - \alpha}{1 - \alpha} \\ + \rho(1 + \alpha) \log \left(1 - f_c \frac{e^{-m\tau} - \alpha}{1 - \alpha} + f_c e^{-k\tau}\right). \end{aligned} \quad (11)$$

This expression is actually very satisfactory if $\rho \lesssim 0.1$, $\alpha \lesssim 0.1$, $f_c \lesssim 0.9$ and if $\Delta \lesssim 0.3$. The last restriction may be removed if Δ_2 is substituted for Δ on the right-hand side of (10) and a third approximation is obtained. Further substitutions do not help since equation (10) is an approximation to (8). The values obtained in this manner are almost indistinguishable from those given in Figure 1.

The parameters may be estimated from experimental data as follows: When τ becomes very large we have from equation (8)

$$\begin{aligned} \Delta(\infty) &= 1 + \frac{\alpha f_c}{(1 + \alpha)^{1/(1-\rho)} \{\rho^{\rho/(1-\rho)} - \rho^{1/\rho}\} - \alpha} \\ &\doteq 1 + \frac{\alpha f_c}{1 + \rho \log \rho - \rho}. \end{aligned} \quad (12)$$

Thus α may be estimated to a first approximation by neglecting the terms in ρ. When τ is large enough ($m\tau \gtrsim 1$), equation (11) reduces to

$$\Delta_2 = \Delta_\infty - f_c(1 - \rho) e^{-m\tau}/(1 - \alpha), \quad (13)$$

where Δ_∞ is $\Delta_2(\tau = \infty)$ and depends upon f_c. Introducing the experimental values for Δ_∞ and f_c and the estimate of α, one can estimate m

to a first approximation by setting $\rho = 0$ in equation (13). With these values of α and m, k can be roughly estimated by trial and error using equation (11). With this estimate, and since $\rho = m/k$, both α and m can be adjusted. Then with the new values for α and m, a corrected value of k can be obtained and $\Delta(f_c, \tau)$ can be computed from (11) or (8).

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A MECHANISM FOR OPTIC NERVE CONDUCTION AND FORM PERCEPTION: II

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This paper continues the analysis of a hypothetical device for "bottleneck" optic nerve conduction and form perception. The neural mechanism described in this paper provides for a form perception which is invariant for transformations of size, translation and rotation on the retina. The number of neurons at different levels in the mechanism is considered.

I. *Form perception invariant for changes in size, position, orientation of the retinal image.*

In a previous paper (Culbertson, 1948, hereinafter denoted by MI) we began the description of a hypothetical retina and nerve net. This description is continued in the present paper, which pre-supposes a knowledge of MI. In MI we showed that if any pattern (activity matrix) occurs in z^l (any one of the $\nu = 100$ square arrays of 225 neurons each at level Z) at any time t, then the same pattern occurred at $t-1$ in some set s^κ of neurons in the synchronized retinas D or D'. The set s^κ consists of all the neurons within some one of the 6.4×10^7 mappings on D and D', the mapping subdividing s^κ by small squares into 225 subsets whose firings at $t-1$ collectively determine the activity matrix $P(s^\kappa, t-1)$, which is called the pattern in s^κ at $t-1$*, i.e., for any values of t and $l = 1, 2, \cdots \nu$ we have $P(z^l, t) = P(s^\kappa, t-1)$ always true for some value of κ.

Remembering that all the ν sets at level Z are identical in structure, and the ν sets at level H are identical in structure and also in the contacts they make with the Z level, we have the following result. Let any light image be projected on the retina so as to cause some pattern in z^l at t such that $P(z^l, t)$ comes from an s^κ having no null subsets (see previous footnote). Also, let all neurons in z^l which fire at t, say there are ω of these, have an excitatory end bulb on some neuron h_ι at level H and all not firing have an absolutely inhibitory bulb in h_ι. Thus, by the structural identity mentioned, there are ν neurons similar to h_ι, one above each z^l. Each is designated h_ι. Let each h_ι have one bulb on some neuron f_ι whose threshold is 1. Then there are $\mathcal{N}^- \cong 6.4 \times 10^7$ changes in position, size, orientation of the image which likewise cause f_ι to fire if each projection lasts $\mathcal{T} = mk\delta \cong 1280$ sec.* Here there are no other end bulbs on h_ι or f_ι, the threshold of h_ι equals the number of excitatory bulbs on it, and $\mathcal{N}^-$, slightly less than $\mathcal{N}$, is the number of distinct mapped sets s^κ without null subsets. As our example, let us again take pattern P_T and define P_T as the activity matrix in Figure 1. Thus

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* A few of the non-upright mappings of the 4 smallest sizes, (those with small squares measuring 1, 1.1, 1.21, and 1.331 units on each side) and a few of the large non-upright mappings at the periphery, will have some small squares not containing any neurons, so that in these cases s^κ contains some null subsets. In the pattern $P(s^\kappa, t-1)$, the activity value of any null subset s_{ij} is defined as zero. Considering the total number of mappings evaluated in MI, we see that a negligible number of small mappings gives identical neuron sets. Thus, rotating any smallest upright mapping through 3.6° or multiplying its area by 1.1, we find the same neurons enclosed, and similarly for some other special cases involving very small mappings. If the same neuron set is given by two mappings, the mechanism funnels the set twice during each cycle period, once for each mapping.

```
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 1 1 1 1 1 1 1 1 1 1 1 0 0
0 0 1 1 1 1 1 1 1 1 1 1 1 0 0
0 0 1 1 1 1 1 1 1 1 1 1 1 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 1 1 1 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

FIGURE 1

$$f_\iota(t+2) \equiv [\textstyle\sum h_\iota(t+1)] \equiv [P(z^l, t) = P_T],$$

where $l = 1, 2, \cdots \nu$. As our "T-shaped" image we take a solid T 11c units across, 11c units high, and 3c units thick through the horizontal and vertical bars so that its area is ωc^2 where $\sqrt{2} \lesseqgtr c \lesseqgtr 333\frac{1}{3}$. In Figure 1 this is shown superimposed on an upright mapping (see the next to the last paragraph in MI). The unit of distance, as mentioned previously, is the distance between two consecutive neurons in any row or column of A or D.

For any T-image projection (thus defined) causing f_ι to fire, we notice that small variations of its position, size, orientation likewise cause f_ι to fire and that, because of the small gradations in the mappings, it is possible to move the image *continuously* from one position, size, orientation causing f_ι to fire to any other causing f_ι to fire (if $c > \sqrt{2}$) so that every intermediate variation of position, size, orientation can cause f_ι to fire.

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* The necessary projection time and hence also the reaction time is, of course, much too large as mentioned in MI. This will be reduced by an accessory "attention" apparatus involving a small number of neurons.

As explained in MI, there were mappings of 123 different sizes. Their areas were $225(1.1)^{\gamma}$ where $\gamma = 0, 1, 2, \cdots 122$. The center squares of equal sized upright mappings did not overlap but filled a square area whose center was the center of D. The number, N_γ, of upright mappings on D of area $225(1.1)^{\gamma}$ was a maximum such that

$$R \geqq N_\gamma \leqq (10 + \gamma)^2$$

where R was the greatest number of upright mappings of area $225(1.1)^{\gamma}$ that could be mapped on D without any overlapping of their center squares. For $\gamma \leqq 81$ the value of N_γ was restricted by the right-hand member of the above expression; for $\gamma > 81$ it was restricted by the left-hand member. Hence, all upright mappings on D of area $225(1.1)^{\gamma}$ are contained within an upright restricting square U_γ which is $(24 + \gamma)^2(1.1)^{\gamma}$ units in area centered on the center of the retina, so that mappings less than $225(1.1)^{82}$ in area are restricted by these squares to less than the entire retina, those greater are restricted by the boundaries of the retina. Thus, the minimum size of a T-image which can cause h_ι to fire is a function of retinal position. The smallest T-image which can be translated from any projection in U_0 effective in firing f_ι to any other effective projection in U_0 continuously, so that each intermediate projection can be effective, has the area ω. In general, a T-image of area $\omega(1.1)^{\gamma}$ can be translated from any effective projection in U_γ to any other effective projection in U_γ continuously, so that each intermediate projection is effective. Also any T-image of area $A \overset{=}{>} \omega(1.1)^{\gamma}$, where $\gamma > 3$, projected within the retinal surface and within U_γ for $\mathcal{T} = mk\delta$, will cause f_ι to fire. That is, any T-image (as defined above) projected on the retina for $mk\delta$ in any position, size, orientation causes f_ι to fire if its area $A \overset{=}{>} \omega(1.1)^{\gamma>3}$ and it falls entirely within the retina and within U_γ. This shows a *theoretically possible* mechanism which indicates in part a solution to the gestalt problem of invariant response to an image of a given shape under position, size and orientation variations. The T-image is, of course, just an example. We must indicate how variation (within any limits we wish to assign) in the shape of the image may result in invariant response. This is done by relaxing the firing conditions for h_ι. Also, we must indicate how there are many different possible classifications of patterns into *forms*. A form is defined as any set of patterns firing the same neuron at level F (the term "shape" will refer to a property of the image). The number μ of forms which can occur in the mechanism equals the number of h neurons contacting each z^l which, because of the way levels F and H are connected, as already described, also equals the number of neurons in level F.

It seems to be, to some extent, a question of how far we want the shape as well as size, position, orientation of each image to be alterable and yet produce an invariant response, and what forms, and how many, we want this mechanism to respond to invariantly. If we decide what we want in regard to these questions, then, within obvious limitations, we can get the desired results. There are limitations on the number of neurons, the number of dendrites and axons per neuron, and the number of synapses per dendrite or cell body.

Arbitrarily we assign $\mu = 50{,}000{,}000$ forms to the mechanism, that is, 50 million classes of patterns in z^l such that the same neuron f is fired by all patterns within any one class and is not fired by any patterns not in that class. (Certain of these classes have some patterns in common, as will be indicated.) The order of $P(z^l, t)$ fixes the number of patterns in this mechanism at 2^{225}.

II. *Neuron economy versus dendrite, axon, and geometric economy.*

For simplicity in explaining the principles involved, we placed no limit on the number of dendrites and axons a neuron could have, nor on the maximum distances between dendrite (or axon) endings of the same nerve cell. Economizing in this nerve net to a maximum of approximately 200 dendrites, to the same maximum for axons, and to plausible limits on the distances mentioned, the consequent alterations involve an increase in the number of neurons in the net (but otherwise no important changes). It is necessary to show that this economy still allows a neuron economy giving a reasonable number of nerve cells.

In Figure 1 in MI, the principle layers in the nerve net are shown. The elements up to level C are in the retina and optic tract. Let us consider them first.

There are $w = 2.5 \times 10^7$ receptor neurons (level A) and these are divided into $m_0 = 25$ subsets, each subset A^λ containing $n_0 = 10^6$ neurons. The cycle contains $m_0 k = 100$ neurons, so that if there is just this one cycle (call it J_1), as assumed for simplicity in MI, then each of the m_0 neurons designated x_λ must have 10^6 end bulbs contacting level B, which is not plausible. Instead of this, we will construct the net so that there are 10,000 similar cycles, $J_1, J_2, \cdots J_{10,000}$, reducing the number of these end bulbs for x_λ to 100, which gives 10^6

cycle neurons. The cycles are synchronized by allowing any one member of J_i to have an end bulb on its successor in J_{i+1} or they may be connected in parallel.

Although the receptor neurons may in theory be assigned in any way to the m_0 subsets, some ways of assigning them give rise to anatomical improbabilities. For instance, suppose that we divided the retina into m_0 equal square areas, each containing n_0 neurons and assigned all neurons within any one square to the same subset A^λ. This requires each cycle to cover widely separated points throughout almost the whole retina as it must extend to each square, and this seems improbable. Also, each cell at the B level must have its m_0 dendrites extend to widely separated points as each must enter a different square, and this likewise seems improbable. However, we may divide the retina into n_0 square areas each containing m_0 neurons and assign each neuron within any square to a different subset. Now each cell at the B level has its m_0 dendrites extend only to points within a square area $1/10^6$ the area of the retina and each cycle may be confined to an area only $1/10^4$ the area of the retina. It is clear that for any hypothetical nerve net such geometrical economy must be satisfied, as well as the numerical economies.

There are $n_0 + m_0 = 1{,}000{,}025 \cong 10^6$ neurons in the optic tract of the mechanism (see level VX) so that in the retina and optic tract there are approximately 2.7×10^7 neurons.

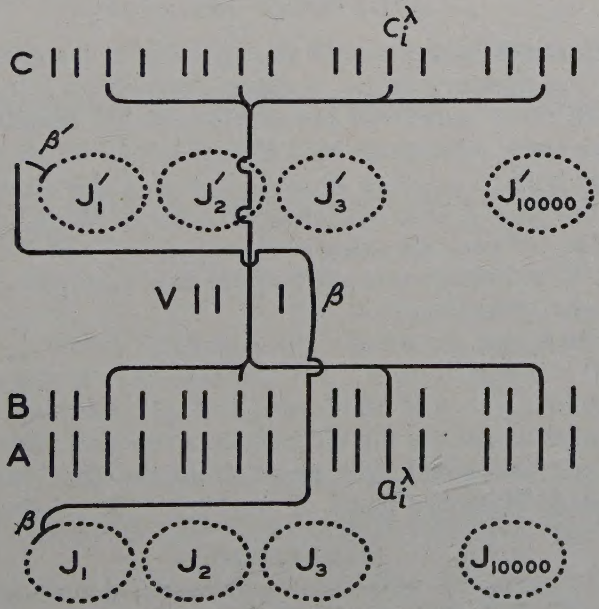

FIGURE 2

Element c_i^λ has the same relative position in C as a_i^λ has in A, so there is geometric as well as numerical economy in the contacts made by the end bulbs of v_i. In MI, however, for simplicity in explaining the principles involved, we gave each x^λ contact with 2×10^6 cells, one excitatory on each member of C and one inhibitory on each circuit between C^λ and D^λ, which is neither geometrically nor numerically economical. We could achieve these economies by introducing a set of internuncials after each x^λ, but there is a simpler symmetrical method shown in Figure 2.

We may remove the entire neuron set X $(x^1, x^2 \cdots x^\lambda \cdots x^{m_0})$ from the nerve net, together with that part of x_λ leading only to x^λ (see Figure 1 in MI) and insert a set of cycles $J_1', J_2' \cdots J'_{10,000}$ exactly similar to the set $J_1, J_2 \cdots J_{10,000}$ and associated with level C. The neuron in J_1' corresponding to β in J_1 is designated β' and β extends through the optic nerve to have an end bulb on β', but there is no other connection between the two sets of cycles.

At any time t (> 0) there is one and only one cell firing in each of the 2×10^4 cycles. The neuron in each J' cycle corresponding to x_λ in each J cycle is designated x^λ. All x_λ fire at the same time and all x^λ fire at the same time (1), but the latter fire one δ after the former (2).

$$\Pi\, x_\lambda(t) \equiv x_\lambda(t), \qquad \text{also} \qquad \Pi\, x^\lambda(t) \equiv x^\lambda(t); \tag{1}$$

$$x^\lambda(t) \equiv x_\lambda(t-1). \tag{2}$$

A trivial adjustment necessary in the above is to take any time that *all* β fire as the time origin, i.e., replace Proposition 1 in MI by $\Pi\, \beta\, (0)$. Then all other numbered propositions in MI remain true. The set J' has the same relation to level C as J has to B, so that if x_λ in J_r has an end bulb in b_i^λ, then x^λ in J_r' has an end bulb on c_i^λ, but in addition x^λ has an end bulb inhibiting the circuit above c_i^λ.

This adds 10^6 neurons associated with set C and the latter contains $w = 2.5 \times 10^7$ neurons while there is a negligible decrease of 24 fibers in the optic nerve.

In a subsequent paper we (1) complete the economy analysis from level C through level F, (2) indicate the classification of the 2^{225} patterns into $\mu = 5 \times 10^7$ forms, and (3) construct the "attention" apparatus to reduce the mechanism's reaction time.

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LITERATURE

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